Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study

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Abstract

Objective To ascertain antepartum predictors of newborn encephalopathy in term infants.
Design Population based, unmatched case-control study.
Setting Metropolitan area of Western Australia, June 1993 to September 1995.
Subjects All 164 term infants with moderate or severe newborn encephalopathy; 400 randomly selected controls.
Main outcome measures Adjusted odds ratio estimates.
Results The birth prevalence of moderate or severe newborn encephalopathy was 3.8/1000 term live births. The neonatal fatality was 9.1%. The risk of newborn encephalopathy increased with increasing maternal age and decreased with increasing parity. There was an increased risk associated with having a mother who was unemployed (odds ratio 3.60), an unskilled manual worker (3.84), or a housewife (2.48). Other risk factors from before conception were not having private health insurance (3.46), a family history of seizures (2.55), a family history of neurological disease (2.73), and infertility treatment (4.43). Risk factors during pregnancy were maternal thyroid disease (9.7), severe pre-eclampsia (6.30), moderate or severe bleeding (3.57), a clinically diagnosed viral illness (2.97), not having drunk alcohol (2.91); and placenta described at delivery as abnormal (2.07). Factors related to the baby were birth weight adjusted for gestational age between the third and ninth centile (4.37) or below the third centile (38.23). The risk relation with gestational age was J shaped with 38 and 39 weeks having the lowest risk.
Conclusions The causes of newborn encephalopathy are heterogeneous and many of the causal pathways start before birth.

Introduction

Newborn encephalopathy is an important clinical problem associated with considerable morbidity and mortality and is central in the assignment of blame in obstetric litigation. Birth prevalence ranges from 1.8 to 7.7 per 1000 term live births.[1–7] Few studies have been population based, most have focused largely on the intrapartum period, most have been small, and many lacked adequate controls.[2–6]

Our pilot study identified new possible associations—such as, a family history of seizures, vaginal bleeding in pregnancy, maternal thyroxine treatment, and maternal pyrexia during labour.[7] The aim of this study was to investigate the role of characteristics before conception and antepartum and intrapartum factors in the aetiology of encephalopathy in the newborn and specifically the hypotheses from the pilot study. We report here on characteristics before conception and antepartum.

Subjects and methods

Between June 1993 and September 1995 we conducted a case-control study of term infants with newborn encephalopathy born in metropolitan Perth, Western Australia (population 1.2 million). All cases of moderate and severe newborn encephalopathy are referred to one of the two tertiary neonatal units in Perth.[7] Cases included in this study were those term babies (≥37 weeks) who, during the first week of life, fulfilled the criteria shown in the box. Infants with Down's syndrome or open neural tube defects were excluded. This definition of newborn encephalopathy differs from that used by many others in that it is broader and does not assume an intrapartum aetiology.[2–6] Deaths in the first week of life were reviewed to ensure that no baby who fulfilled the entrance criteria died before transfer.

The severity of newborn encephalopathy was graded as moderate or severe according to criteria modified from Sarnat and Sarnat.[8] Infants with severe encephalopathy were those who fulfilled one or more

Inclusion criteria for cases with moderate or severe newborn encephalopathy

- Either seizures alone or
- Any two of the following lasting for longer than 24 hours:
  - Abnormal consciousness
  - Difficulty maintaining respiration (of presumed central origin)
  - Difficulty feeding (of presumed central origin)
  - Abnormal tone and reflexes

Editorial by Edwards

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Criteria for severe encephalopathy
- Ventilation for >24 hours
- Two or more anticonvulsant treatments
- Comatose or stuporous
- Died in the neonatal period

of the criteria listed in the box; the remainder were defined as moderate.

Controls were randomly selected from the population of term births delivered in metropolitan Perth during the same period; 412 were selected. With 150 to 180 cases the study had ≥90% power to detect a relative risk of 2.5 or more for exposures with a prevalence of between 10% and 85% in the controls.

A questionnaire completed by the mothers collected sociodemographic and lifestyle information together with a medical and family history. Medical details were extracted from medical records. The infants with encephalopathy were examined daily (by NB) and the first 200 control infants were examined at recruitment (by NB).

Statistical analysis

Analyses were carried out with unconditional logistic regression.

Before conception and antepartum—A model containing variables from before conception and the antepartum period was constructed as follows. Explanatory variables were included if there was strong pre-existing evidence that they were causally related to newborn encephalopathy or cerebral palsy or if their inclusion covered a principal hypothesis. Other potential confounding variables were then entered altogether as additional terms in the core model. The additional terms were removed in ascending order of the likelihood ratio test (twice the change in the log likelihood) and all terms which did not represent a significant ($P<0.05$) component of the model were removed. Non-linearity in the continuous variables and interactions were tested for.

Intrapartum—The aetiology of newborn encephalopathy probably involves numerous determinants acting along complex causal sequences. If one is interested in whether factor C causes disease D and, in truth, A causes B causes C causes D, an apparently "complete" logistic regression analysis which mutually adjusts for the effects of A, B, and C by including all three as covariates may be seriously misleading. The strength of the true association between C and D is likely to be underestimated, and if C is "measured" with more error or with greater misclassification than either A or B, disease D may appear independent of C. We therefore adopted a cautious approach to analysis. We estimated bivariate associations between intrapartum variables and the binary variable of newborn encephalopathy (yes/no) with unconditional logistic regression. Each model was restricted to the covariate of interest. This analysis was extended by creating a core model containing all antepartum variables of importance (see table 2). The intrapartum exposures of interest were added to (and removed from) this core model one at a time. An association which is present in *both* the unadjusted and adjusted analyses will be misleading only if it has been confounded by antepartum variables not included in the core model or by intrapartum determinants arising spontaneously or as a direct consequence of unmodelled antepartum exposures. For unmodelled antepartum or intrapartum determinants to distort our inferences seriously their effect would not only have to be substantial but their distribution at a population level would have to be correlated with a covariate of interest. We would therefore argue that any covariate which exhibits an association in both the adjusted and unadjusted analyses is worth considering as a putative cause of newborn encephalopathy. Furthermore, an intrapartum exposure which exhibits an important association with newborn encephalopathy in *either* the adjusted *or* the unadjusted analysis is worthy of further investigation with independent data. The findings of the intrapartum analysis are reported in the accompanying paper.[9]

Results

In total we enrolled 164 infants with encephalopathy as cases and 400 infants as controls, a response of 100% and 97%, respectively. The birth prevalence of moderate or severe newborn encephalopathy was 3.80 per 1000 term live births (95% confidence interval 3.24 to 4.43). Fifteen case infants and no control infants died in the neonatal period, giving a neonatal case fatality of 9.1% (5.2% to 14.6%). Table 1 gives the observed distribution of the entry criteria for the affected infants, two thirds of whom had moderate encephalopathy and a third had severe encephalopathy.

Table 1 Features of encephalopathy among 164 case infants

Features	No of cases*
Seizures	109
Abnormal tone	148
Apnoeas	93
Feeding difficulties	146
Abnormal consciousness	159
Requiring ventilatory support	50

*Categories not mutually exclusive.

Factors before conception

Risk factors from before conception and antepartum risk factors for newborn encephalopathy are shown in table 2.

Sociodemographic factors—The adjusted relative risk of newborn encephalopathy increased significantly with increasing maternal age. Rather than risk increasing with parity, there was a non-significant decrease in risk of 17% for each delivery after the first (odds ratio 0.83; 95% confidence interval 0.64 to 1.06). Infants born to professional women, trades persons, or clerks were at least risk with other forms of employment and unemployment being associated with an increased relative risk. Interestingly, paternal employment status had no additional effect. Women without private health insurance were at a greater risk than those with such insurance.

Medical conditions—A family history of recurrent non-febrile seizures or other neurological disorders, defined as any mention of these conditions in up to second degree relatives of the child, were associated

with over a 2.5-fold increase in relative risk. Infertility treatment was associated with over a fourfold increased risk. Essential hypertension was associated with a non-significant increased risk.

Antepartum factors

Maternal conditions—Women with thyroid disease were over nine times more likely to have a baby with newborn encephalopathy than those without. Severe pre-eclampsia, moderate or severe vaginal bleeding in pregnancy, and a documented medical attendance for a presumed viral infection were all associated with an increased risk. While nearly all women reported drinking very little or no alcohol during pregnancy consumption of some alcohol was apparently protective. Cigarette smoking showed no effect.

Infant characteristics—The relative risk in relation to gestational age showed a clear J shaped curve ranging from 2.35 at 37 weeks' to 13.2 at 42 weeks' gestation. Growth restriction[11] was also strongly associated with the risk of newborn encephalopathy. Boys were at a 50% increased risk compared with girls, which was almost significant. The presence of a placenta reported as abnormal at birth was associated with a doubling in risk. Six affected infants and one control infant had late or no antenatal care. There was a non-significant increase in risk for births at a private hospital. There were too few twins to draw conclusions. Several variables were not included as they were possibly along a causal pathway or were outcome variables associated with newborn encephalopathy. Inclusion of these variables in the adjusted analysis would have potentially masked the effects of other variables that were working in combination with them. These variables included birth defects (found in 23.2% affected infants and 2.3% control infants) and a reported abnormal antepartum cardiotocogram (found in 8.5% and 2.0%, respectively).

Table 2 Risk factors from before conception and antepartum period for newborn encephalopathy

Risk factor	No (%) of cases (n=164)	No (%) of controls (n=400)	Unadjusted odds ratio	Adjusted odds ratio* (95% CI)
Before conception				
Maternal age (years):				
<20	5 (3.0)	20 (5.0)	1†	1†
20-24	32 (19.5)	54 (13.5)	2.37	4.21 (1.01 to 17.50)
25-29	60 (36.6)	130 (32.5)	1.85	5.91 (1.42 to 24.54)
30-34	41 (25.0)	125 (31.3)	1.31	6.71 (1.53 to 29.44)
≥35	26 (15.9)	71 (17.7)	1.46	6.01 (1.28 to 28.15)
Parity:				
0	76 (46.3)	168 (42.0)	1.14	1.81 (0.87 to 3.73)
1	48 (29.3)	131 (32.8)	0.93	1.15 (0.58 to 2.28)
≥2	40 (24.4)	101 (25.3)	1†	1†
Maternal employment:				
Professional	29 (17.7)	111 (28.7)	1†	1†
Trade or clerical	43 (26.2)	150 (37.5)	1.09	1.26 (0.63 to 2.50)
Unskilled manual	14 (8.5)	15 (3.7)	2.35	3.84 (1.43 to 10.28)
Housewife	46 (28.1)	75 (18.7)	3.57	2.48 (1.14 to 5.39)
Unemployed	14 (8.5)	12 (3.0)	4.47	3.60 (1.10 to 11.80)
Missing	18 (11.0)	37 (9.2)	1.86	0.93 (0.33 to 2.60)
Health insurance:				
Private	42 (25.6)	173 (43.2)	1†	1†
Public	122 (74.4)	227 (56.7)	2.21	3.46 (1.25 to 9.59)
Maternal race:				
White	142 (86.5)	372 (93.0)	1†	1†
Aboriginal	10 (6.1)	12 (3.0)	2.18	0.75 (0.21 to 2.72)
Other	12 (7.0)	16 (4.0)	1.96	1.54 (0.58 to 4.10)
Family history of seizures‡:				
No	131 (79.9)	365 (91.3)	1†	1†
Yes	33 (20.1)	35 (8.7)	3.10	2.55 (1.31 to 4.94)
Family history of neurological disorders§:				
No	147 (89.6)	383 (95.8)	1†	1†
Yes	17 (10.4)	17 (4.2)	2.61	2.73 (1.16 to 6.41)
Infertility treatment:				
No	156 (95.1)	391 (97.8)	1†	1†
Yes	8 (4.9)	9 (2.2)	2.23	4.43 (1.12 to 17.60)
Maternal hypertension:				
No	155 (95.5)	391 (97.8)	1†	1†
Yes	9 (5.5)	9 (2.2)	2.50	2.41 (0.74 to 7.79)
Maternal height (cm):				
<160	43 (26.2)	94 (23.5)	1.22	0.98 (0.57 to 1.70)
160-164	64 (39.0)	154 (38.5)	1†	1†
>164	57 (34.8)	152 (38.0)	1.11	0.79 (0.43 to 1.43)

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Discussion

Many previous studies of newborn encephalopathy have been restricted to babies who showed so called signs of hypoxia and ischaemia during labour. As the present study aimed to investigate a wider range of potential causes we chose a broader though widely accepted definition of newborn encephalopathy and investigated factors from before conception to postnatal events.

Intrauterine growth restriction, pre-eclampsia, and gestational age

The association of newborn encephalopathy with restriction of intrauterine growth was the strongest found in this analysis. Similar associations have been described for cerebral palsy,[12 13] seizures in the newborn, and encephalopathy.[7 14] This association shows the importance of the selection of our study population by gestational age rather than birth weight. If "term" had been defined by birth weight (for example, ≥2500 g) the significance of growth restriction to encephalopathy may have been underestimated.

Different causes of growth restriction may differ in their capacity to cause newborn encephalopathy or to predispose a fetus to the damaging effects of an intermediate factor. Although pre-eclampsia is a common cause of growth restriction, it was an important independent risk factor for encephalopathy in this and other studies,[2 15] although there is not a consistently reported association with cerebral palsy.[16]

The exponential rise in relative risk from 39 to 42 weeks' gestation confirmed the findings of the pilot study and other studies.[5 7] Animal studies have shown that post-term fetuses are most vulnerable to asphyxia.[17] This finding is important in the context of the recent debate about recommendations for induction at 41 weeks.[18]

Sociodemographic factors

We found a range of social and demographic factors that have not previously been described as risk factors for newborn encephalopathy. Contrary to expectations the risk with increasing maternal age does not seem to be mediated through increasing parity. The strong correlation between maternal age and parity, however, makes it difficult to disentangle their individual effects,

Table 2 *Continued*

Risk factor	No (%) of cases (n=164)	No (%) of controls (n=400)	Unadjusted odds ratio	Adjusted odds ratio* (95% CI)
Antepartum				
Maternal thyroid disease:				
No	157 (95.7)	397 (99.3)	1†	1†
Yes	7 (4.3)	3 (0.7)	5.9	9.70 (1.97 to 47.91)
Pre-eclampsia¶:				
No	127 (77.4)	343 (85.8)	1†	1†
Mild	21 (12.8)	46 (11.5)	1.23	1.62 (0.80 to 3.27)
Severe	16 (9.8)	11 (2.8)	3.93	6.30 (2.25 to 17.62)
Bleeding (moderate or severe):				
No	153 (93.3)	388 (97.0)	1†	1†
Yes	11 (6.7)	12 (3.0)	2.32	3.57 (1.30 to 9.85)
Viral illness:				
No	138 (84.1)	361 (90.3)	1†	1†
Yes	26 (15.9)	39 (9.7)	2.10	2.97 (1.52 to 5.80)
Alcohol consumption:				
Some	45 (27.4)	135 (33.7)	1†	1†
None	102 (62.2)	228 (57.0)	1.34	2.91 (1.70 to 5.00)
Missing	17 (10.4)	37 (9.3)	1.03	6.38 (2.33 to 17.51)
Gestational age (weeks):				
37	11 (6.7)	19 (4.8)	1.44	2.35 (1.11 to 4.97)
38	35 (21.3)	79 (19.8)	1.10	1.18 (0.90 to 1.56)
39	31 (18.9)	77 (19.3)	1†	1†
40	39 (23.8)	170 (42.5)	0.57	1.41 (1.17 to 1.70)
41	32 (19.5)	45 (11.3)	1.77	3.34 (2.09 to 5.35)
42	16 (9.8)	10 (2.5)	3.97	13.2 (5.03 to 34.83)
Centile birth weight**:				
>90th	14 (8.5)	44 (11.0)	1†	1†
10th-90th	114 (69.5)	322 (80.5)	1.11	1.54 (0.66 to 3.62)
3rd-9th	15 (9.2)	29 (7.2)	1.63	4.37 (1.43 to 13.38)
<3rd	21 (12.8)	5 (1.2)	13.2	38.23 (9.44 to 154.79)
Infant's sex:				
Female	70 (42.5)	203 (50.8)	1†	1†
Male	94 (57.5)	197 (49.2)	1.38	1.56 (0.97 to 2.49)
Appearance of placenta:				
Normal or missing	120 (73.2)	355 (88.8)	1†	1†
Abnormal	44 (26.8)	45 (11.2)	3.21	2.07 (1.15 to 3.73)
Late or no antenatal care:				
No	158 (96.3)	399 (99.8)	1†	1†
Yes	6 (3.7)	1 (0.2)	15.14	5.45 (0.47 to 62.98)
Hospital of delivery:				
Tertiary	55 (33.5)	70 (17.5)	1†	1†
Private	35 (21.3)	151 (37.8)	0.30	1.71 (0.60 to 4.88)
Public+BBA††	74 (45.2)	179 (44.8)	0.53	1.08 (0.59 to 1.97)
Plurality:				
Singletons	160 (97.6)	398 (99.5)	1†	1†
Twins	4 (2.4)	2 (0.5)	4.97	1.04 (0.11 to 9.55)

*Adjusted for effects of all other variables in table. †Baseline comparison group.
‡Recurrent, non-febrile seizures. §Excludes seizures.
¶Pre-eclampsia defined as systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg, or both, or rise in systolic blood pressure ⩾25 mm Hg or rise in diastolic blood pressure ⩾15 mm Hg, or both, from blood pressure readings before conception or in first trimester (confirmed by two readings 6 hours apart). Severe pre-eclampsia was defined as any of: blood pressure of ⩾170 mm Hg systolic or blood pressure ⩾110 mm Hg diastolic, or both, proteinuria >300 mg or ⩾2+ with dipstick testing, serum creatinine >0.09 mmol/l, epigastric pain, rasied bilirubin or transaminases, or both, persistent headaches, visual disturbance, hyper-reflexia or clonus, or both.[10]
**Birth weight adjusted for gestation, parity, maternal height, and infant's sex.[11]
††Two case infants (1.3%) and no control infants were born before arrival at hospital (BBA).

and these results should therefore be interpreted with caution.

The mechanism of action of socioeconomic circumstances, as defined by employment and private health insurance, requires further investigation and careful interpretation as they may not have the same impact in different populations. Nevertheless, they certainly deserve more attention than they have received to date. The beneficial effect of drinking some alcohol in pregnancy is also interesting as most women in the study drank small amounts, which may reflect social advantage rather than the effect of alcohol per se. Given recent research on the benefits of small amounts of alcohol in other diseases,[19] however, this merits further study.

Other antepartum factors

A family history of seizures and of other neurological disorders were confirmed as risk factors and have been described in studies of cerebral palsy and neonatal seizures.[20] These results suggest that genetic or early developmental factors may influence the risk of newborn encephalopathy.

The association between newborn encephalopathy and infertility treatment was a new finding. Children born after infertility but before modern treatments did not have an increased risk of cerebral palsy.[20] Couples with infertility, however, now have a greater chance of conceiving, and there is evidence to suggest an increased risk of cerebral palsy associated with in vitro fertilisation.[21]

Maternal thyroid disease was confirmed as a risk factor and has been reported in cerebral palsy.[20 22] It is entirely plausible that maternal thyroid dysfunction, its aetiology, or aspects of its treatment may lead to disorders of fetal neuronal development which result in newborn encephalopathy and cerebral palsy.

Bleeding in pregnancy was a risk factor in the pilot study and has been reported in association with hypoxic-ischaemic encephalopathy[2] and cerebral palsy.[23] The role of perinatal infection is of considerable aetiological interest in neurological dysfunction in preterm[24] and term[25] infants. In addition to the well known viral teratogens (rubella, cytomegalovirus) other viruses may be teratogenic or other mechanisms may operate—such as hyperthermia,[26] inflammatory mediators, or other pathophysiological responses.[27] Evidence from this and other studies suggests that the placenta may be an important but currently ignored (and commonly discarded) source of information.

Data from infants with birth defects and abnormal antepartum cardiotocograms were deliberately excluded from the multiple logistic regression analysis. While numbers were small the excess of abnormal antepartum cardiotocograms in case infants suggests the presence of antepartum compromise. Case infants had excess malformations and most were not defects of the central nervous system, findings consistent with results of other studies.[3 7 28] Birth defects occur early in intrauterine life and may be markers of factors in early pregnancy, which may also cause the encephalopathy. Alternatively a birth defect may make the fetal brain vulnerable to other damaging factors.

Our definition of encephalopathy was broad, the study was population based, control data were collected, and the results suggest that the causes of newborn encephalopathy are heterogeneous and that many of the causal pathways resulting in newborn encephalopathy start before birth.

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Key messages

- The birth prevalence of moderate or severe newborn encephalopathy was 3.8 per 1000 term live births and the neonatal case fatality was 9.1%
- Independent risk factors before conception and in the antepartum period for newborn encephalopathy include socioeconomic status, family history of seizures or other neurological disease, conception after infertility treatment, maternal thyroid disease, severe pre-eclampsia, bleeding in pregnancy, viral illness, having an abnormal placenta, intrauterine growth restriction, and postmaturity
- The causes of newborn encephalopathy are heterogeneous and many causal pathways start in the antepartum period

Contributors: NB designed the study, obtained a research training fellowship which funded the start of the project, was chief investigator on the subsequent research grant which funded its continuation, enrolled cases and half the controls and collected the data relating to these, coded the data, entered data into the file for analysis, carried out the analysis, and wrote the first draft of the paper. JJK assisted with the design of the study, particularly the control selection method, assisted with data coding and computerisation, and supervised the analysis and writing of the paper. JMK assisted with the obstetric elements of the design of the study, facilitated data collection, provided expert obstetric interpretation of the data, and contributed to the paper writing. LMA assisted with the supervision of the pilot study and the design of this study, contributed to the day to day running of the study, and assisted with data handling and interpretation. Sadly, her untimely death precluded her from contributing to the writing of the paper. FO enrolled and collected original data from half the controls and collected data from cases and controls for the data validation, and also edited the paper. PRB provided advice at every stage of the study, oversaw the analytical strategy, and provided editorial direction during writing. PJP assisted with the study design, helped enrol cases, and edited the paper. FJS had the original idea for the present study, assisted with the design, and contributed to the writing and editing of the paper. NB and JK are the guarantors.

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1 Nelson KB, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? *Am J Dis Child* 1991;145:1325-31.
2 Finer NN, Robertson CM, Richards RT, Pinnell LE, Peters KL. Hypoxic-ischemic encephalopathy in term neonates: perinatal factors and outcome. *J Pediatr* 1981;98:112-7.
3 Ergander U, Eriksson M, Zetterstrom R. Severe neonatal asphyxia—incidence and prediction of outcome in the Stockholm area. *Acta Paediatr* 1983;72:321-5.
4 Levene ML, Kornberg J, Williams THC. The incidence and severity of post-asphyxial encephalopathy in full-term infants. *Early Hum Develop* 1985;11:21-6.
5 Hull J, Dodd KL. Falling incidence of hypoxic-ischaemic encephalopathy in term infants. *Br J Obstet Gynaecol* 1992;99:386-91.
6 Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. *Acta Paediatr* 1995;84:927-32.
7 Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley FJ. Predictors of neonatal encephalopathy in full term infants. *BMJ* 1995;311:598-602.
8 Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. *Arch Neurol* 1976;33:696-705.
9 Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998:317:1554-8.
10 Consensus statement. Australasian Society for the Study of Hypertension in Pregnancy. Management of hypertension in pregnancy: executive summary. *Med J Aust* 1993;158:700-2.
11 Blair E, Stanley FJ. *Intrauterine growth charts for singleton liveborn West Australian infants*. Canberra: Australian Government Printer, 1985.
12 Blair E, Stanley FJ. Intrauterine growth and spastic cerebral palsy. I. Association with birth weight for gestational age. *Am J Obstet Gynecol* 1990;162:229-37.
13 Gaffney G, Sellers S, Flavell V, Squier M, Johnson A. Case-control study of intrapartum care, cerebral palsy, and perinatal death. *BMJ* 1994;308: 743-50.
14 Dennis J. Neonatal convulsions: aetiology, late neonatal status and long-term outcome. *Dev Med Child Neurol* 1978;20:143-58.
15 Gaffney G, Flavell V, Johnson A, Squier M, Sellers S. Cerebral palsy and neonatal encephalopathy. *Arch Dis Child* 1994;70:F195-200.
16 Nelson, KB, Grether J. Cerebral palsy in very low birth weight infants, pre-eclampsia and magnesium sulphate. *Pediatrics* 1995;95:263-9.
17 Mallard EC, Williams CE, Johnston BM, Gluckman PD. Increased vulnerability to neuronal damage after umbilical cord occlusion in fetal sheep with advancing gestation. *Am J Obstet Gynecol* 1994;170:206-14.
18 Hannah ME, Hannah WJ, Hellmann J, Hewson S, Milner R, Willan A. Induction of labour as compared with serial antenatal monitoring in post-term pregnancy: a randomised controlled trial. *N Engl J Med* 1992;326:1587-92.
19 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine or spirits? *BMJ* 1996;312:731-6.
20 Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. *Am J Dis Child* 1985;139:1031-8.
21 Kurinczuk JJ, Webb S, Burton PR, Stanley FJ. Childhood outcomes associated with assisted conception procedures. *Paediatr Perinat Epidemiol* 1995;9:A9.
22 Blair E, Stanley FJ. When can cerebral palsy be prevented? The generation of causal hypotheses by multivariate analysis of a case-control study. *Paediatr Perinat Epidemiol* 1993;7:272-301.
23 Hagberg G, Hagberg B, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. III. The importance of foetal deprivation of supply. *Acta Paediatr* 1976;65:403-8.
24 Leviton A. Preterm birth and cerebral palsy: is tumour necrosis factor the missing link? *Dev Med Child Neurol* 1993;35:553-8.
25 Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA* 1997;278:207-11.
26 Halperin LR, Wilroy RS. Maternal hyperthermia and neural-tube defects [letter]. *Lancet* 1978;2:212-3.
27 Adinolfi M. Infectious diseases in pregnancy, cytokines and neurological impairment: an hypothesis. *Dev Med Child Neurol* 1993;35:549-58.
28 Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 1986;315:81-6.

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Fifty years ago

The new NHS: Too many or too few?

Could you please tell me whether there are too many doctors or too few? I ask this somewhat naive question simply because I am genuinely bewildered about the matter. On the one hand we have the sponsors of the National Health Service warning the public not to expect the full benefits of the scheme just yet owing to the grave shortage of doctors, nurses, health centres, etc., while on the other hand it is pretty obvious to those of us who are not hypocrites that newly established practitioners who joined the Service after the general rush to "sign on" with doctors are likely to be in for a lean time. I know that this view is shared by at least one important official employed by the London Executive Council, and I myself know of several such newly established practitioners who are still sitting in their newly painted surgeries with very little to do, very few patients on their list, and very little money to support their families on.—I am, etc., London SW3, Victor Constad.

(*Letter*, 18 September 1948, p 26(suppl). See also editorial by Gordon Macpherson, 3 January 1998, p 6.)